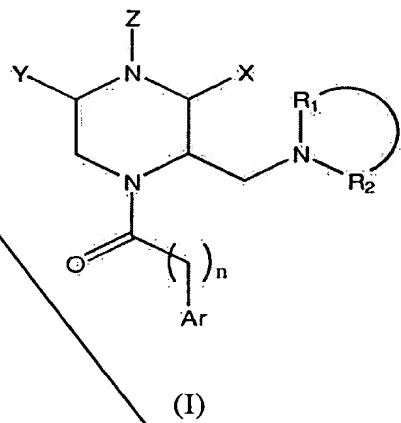


WHAT IS CLAIMED IS:

1 A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula I or a pharmaceutically acceptable salt thereof



5 wherein

n = 1-3;

R₁ and R₂ are independently $-\text{CH}_3$; $-(\text{CH}_2)_m$, where m =

4-8, $-\text{CH}_2\text{CH}(\text{OH})(\text{CH}_2)_2$; $-\text{CH}_2\text{CH}(\text{F})(\text{CH}_2)_2$;

$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; or $-(\text{CH}_2)_2\text{CH}=\text{CHCH}_2$;

10 Ar = unsubstituted or mono-, or di-substituted phenyl

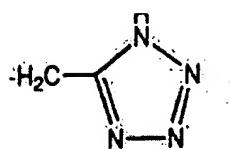
wherein said substituents are selected from the group

consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

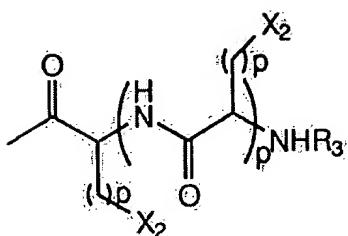
15 Z is

$-\text{P}(\text{O})(\text{OBn})_2$; $-\text{P}(\text{O})(\text{OH})_2$; $-(\text{CH}_2)_p\text{C}(\text{O})\text{NHOH}$; $-(\text{CH}_2)_p\text{CO}_2\text{H}$; $-\text{SO}_2\text{CH}_3$; $-\text{SO}_2\text{NH}_2$; $\text{CO}(\text{CH}_2)_p\text{CH}(\text{NH}_2)(\text{CO}_2\text{H})$; $-\text{COCH}(\text{NH}_2)(\text{CH}_2)_p\text{CO}_2\text{H}$; $-\text{CO}_2\text{CH}_3$; $-\text{CONH}_2$; $-(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CO}_2\text{H}$; $-(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CONHOH}$; $-(\text{CH}_2)_p\text{NHSO}_2\text{CH}_3$; $-(\text{CH}_2)_p\text{NHC}(\text{S})\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_p\text{CO}_2\text{H}$; $-(\text{CH}_2)_p\text{SO}_3\text{H}$; or

or Z is



wherein



$p = 0 - 20$

$R_3 = -H$ or $-Ac$;

$X_2 = -CO_2H$; $-NHSO_2CH_3$; $NHP(O)(OBn)_2$; $NHP(O)(OH)_2^-$;
 $OP(O)(OBn)_2$; or $OP(O)(OH)_2$

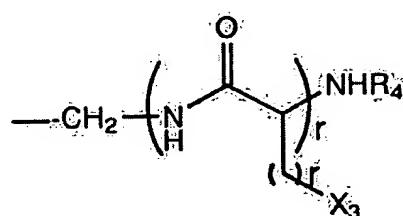
X and Y are independently

$-CH_2NHSO_2CH_3$, $-CH_2NHP(O)(OBn)_2$, $-CH_2NHRO(OH)_2$, -

$CH_2OP(O)(OBn)_2$, $CH_2OP(O)(OH)_2$, $(CH_2)_qO(CH_2)_qCO_2H$,

$(CH_2)_qO(CH_2)_qSO_3H$, $(CH_2)_qO(CH_2)_qCHNHOH$,

$CH_2NHC(S)NHCH(CO_2H)(CH_2)_qCO_2H$, or



wherein

$q = 1-20$

$r = 1-20$

$R_4 = -H$ or $-Ac$

5 $X_3 = -CO_2H; -NHSO_2CH_3; -NHP(O)(OBn)_2;$
 $-NHP(O)(OH)_2; -OP(O)(OBn)_2;$ or
 $-OP(O)(OH)_2$

in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1 wherein said compound is
10 selected from the group consisting of: (4-[1-(3,4-Dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)-
methyl]piperazinyl)acetic acid; [1-(3,4-Dichlorophenyl)acetyl-4-methanesulfonyl-2R-(1-
pyrrolidinyl)methyl]piperazine; [4-S-Aspartic acid- α -amido-1-(3,4-dichlorophenyl)acetyl-
2R-(1-pyrrolidinyl)methyl]piperazine; Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-
dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[2R-(O-
15 S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-
pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-
methanesulfonamido)aminomethyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate;
Methyl-{4-[3,4-dichlorophenyl]acetyl-3R-[1-pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-
thioureido)aminomethyl-1-piperazinecarboxylate; Methyl-[2S-(O-2-acetic
20 acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-
piperazinecarboxylate; Methyl-[2S-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-
dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-
dichlorophenyl)acetyl-2S-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-
25 1-piperazinecarboxylate; Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl]methyl-
2S-[N-(succinic acid-2S-thioureido)]aminomethyl-1-piperazinecarboxylate; Methyl-[2R-(O-
2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-
piperazinecarboxylate; Methyl-[2R-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-
dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-
30 dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-
1-piperazinecarboxylate; and Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-
pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-thioureido)]aminomethyl}-1-
piperazinecarboxylate.

3. The pharmaceutical composition according to claim 1 wherein said compound is
selected from the group consisting of:

(*R*)-4-(Phenylmethyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;

(*R*)-1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;

(*R*)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R*)-4-t-Butyl-acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]- piperazine;

(*R*)-4-(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazineacetic acid dihydrochloride;

(*R*)-4-N-t-Boc-D-aspartic acid- β -benzyl ester-1 -[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine;

(*R*)-4-Aspartic acid-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine dihydrochloride;

(*R*)-4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R*)-4-(Diethoxyphosphonate)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R*)-4-Trifluoroacetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R*)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxamide hydrochloride;

(*R*)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxaldehyde hydrochloride;

(*R*)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazine-sulfonamide hydrochloride;

(*R*)-4-(4-Methylphenylsulfonyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl] -piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-methylsulfonylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

5 (*R,S*)-4-Methanesulfonyl-1-[(2-nitrophenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-trifluoromethylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

10 (*R,S*)-4-Methanesulfonyl-1-[(3-indolylacetyl)-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-Methyl 4-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

(*R,S*)-Methyl 4-[(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

15 (*R,S*)-Methyl 4-[(3-indolyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

20 (*R,S*)-Methyl 4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-aminophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate dihydrochloride;

(*R,S*)-4-Acetyl-1-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-piperazine hydrochloride;

25 (*R,S*)-4-Acetyl-1-(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

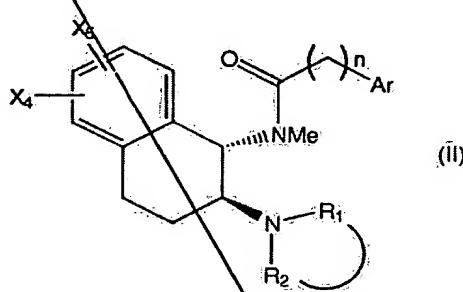
(*R,S*)-4-Acetyl-1-[(2-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(3-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

5 (*R,S*)-4-Acetyl-1-[(4-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine; carboxylate hydrochloride; and

(*R,S*)-4-(Phenylmethyl)-1-[(4,5,-dichloro-2-nitrophenyl)acetyl]-2-[(1-



pyrrolidinyl)methyl]piperazine dihydrochloride.

4. A method for the prevention or treatment of pruritus in a patient comprising 10 administering to said patient an effective amount of a composition according to claim 1.

5. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 2.

6. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 3.

15 7. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula II or a pharmaceutically acceptable salt thereof wherein

$n = 1-3$;

R_1 and R_2 are independently $= CH_3$; $-(CH_2)_m$, where $m =$

20 $4-8$, $-CH_2CH(OH)(CH_2)_2$; $-CH_2CH(F)(CH_2)_2$;

$-(CH_2)_2O(CH_2)_2$; or $-(CH_2)_2CH=CHCH_2$;

Ar = unsubstituted or mono-, or di-substituted phenyl wherein said substituents are selected from the group consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

25

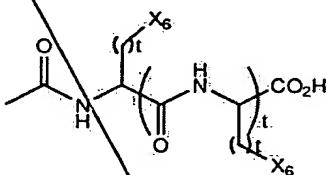
X₄ and X₅ are independently

-OP(O)(OBn)₂ -OP(O)(OH); -CO₂H; -SO₃H; -O(CH₂)_nCO₂H;

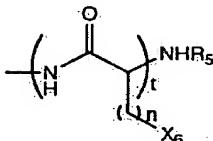
-NHSO₂CH₃; -CONH(CH₂)_sCO₂H; or -SO₂NH(CH₂)_sCO₂H; wherein

s = 1-5

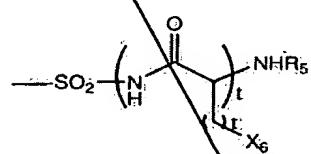
5 or X₄ and X₅ are independently



; or



; or



10 wherein

t = 1-20

15 R₅=-H or -Ac

X₆ = -CO₂H; -NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂; -OP(O)(OBn)₂; or
-OP(O)(OH)₂

in a pharmaceutically acceptable carrier.

8. The pharmaceutical composition according to claim 7 wherein said compound is

20 selected from the group consisting of: (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide; (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; and (±)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide.

9. The pharmaceutical composition according to claim 7 wherein said compound is selected from the group consisting of:

2-(7-[\pm]-trans-1-(N-3,4-dichlorophenylacetamido-N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy} acetic acid;

2,2-Diphenyl-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-methoxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

5 2,2-Diphenyl-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-hydroxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

10 2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-amino-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

15 2-(4-Methylsulfonylphenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(t-butoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

20 2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(carboxymethyl)amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(ethoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

25 2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-(N-diethylphosphoramidato-amino)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-[1-pyrrolidinyl]-7-[N-2-(diethylphosphoryl)ethyl-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-6-methoxy-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;

2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;

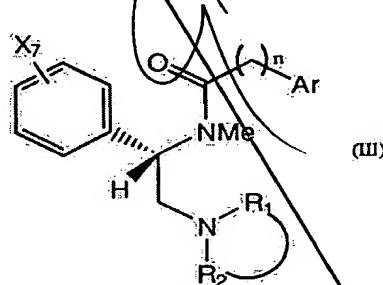
5 2,2-Diphenyl-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide; and
2-(4-Methylsulfonylphenyl)-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide.

10. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 7.

11. A method for the prevention or treatment of pruritus in a patient comprising
10 administering to said patient an effective amount of a composition according to claim 8.

12. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 9.

13. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of the formula III or a pharmaceutically acceptable salt thereof



15 wherein

$n = 1-3$;

R_1 and R_2 are independently $= CH_3$; $-(CH_2)m$, where $m = 4-8$,
 $-CH_2CH(OH)(CH_2)_2$; $-CH_2CH(F)(CH_2)_2$; $-(CH_2)_2O(CH_2)_2$; or
 $-(CH_2)_2CH=CHCH_2$;

20 $Ar =$ unsubstituted or mono-, or di-substituted phenyl wherein said substituted are selected from the group consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

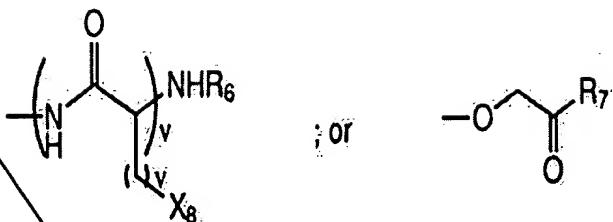
X_7 is

25 $-NHSO_2CH_3$; $-NHP(O)(OBn)_2$; $-NHP(O)(OH)_2$; $-(CH_2)_uNHSO_2CH_3$;
 $-(CH_2)_uNHC(S)NHCH(CO_2H)(CH_2)_uCO_2H$; $-CONHOH$; or $-(CH_2)_uCONHOH$;

wherein

$u = 1-5$; or

X_7 is



$R_6 = -H$ or $-Ac$;

$X_8 = -CO_2H$; $-NHSO_2CH_3$; $-NHP(O)(OBn)_2$;

$-NHP(O)(OH)_2$; $OP(O)(OBn)_2$ or

$-OP(O)(OH)_2$;

$R_7 = -NH(CH_2)_vCO_2H$; -

$NH(CH_2)_vCH(NH_2)(CO_2H)$;

$-NHCH(CO_2H)(CH_2)_vNH_2$; $NH(CH_2)_vSO_3H_2$;

$-NH(CH_2)_vPO_3H_2$; -

$NH(CH_2)_vNHC(NH)NH_2$; or

$-NHCH(CO_2H)(CH_2)_vCO_2H$; and

$v = 1-20$;

5 in a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 wherein said compound is selected from the group consisting of:

2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)carboxamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-1-[3-(N-

10 methanesulfonamido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-succinic acid-2S-thioureido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; and 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)sulfonamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide.

15. The pharmaceutical composition according to claim 13 wherein said compound is

15 selected from the group consisting of:

2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[N-(S-aspartic acid- α -amide-S-aspartic acid-a-amido)-3-aminophenyl]-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[N-(bis-methylsulfonamido)-3-aminophenyl]-2-(1-pyrrolidinyl)ethyl]acetamide;

5 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N-Diethyl phosphoramidate-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N-Bis-sulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-bis-sulfonamido-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

10 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

15 2-(N-Butyloxycarbonyl-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

20 2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;

25 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

(2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

5 2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide;

2,2-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

N',N'-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl] urea;

2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

10 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Methoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

15 2-(3-Indolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(α,α,α -Trifluoro-p-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Nitro- α,α,α -Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

21 2-(1-[4-Chlorobenzoyl]-5-methoxy-2-methyl indole)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

20 2-(4-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

22 2-((+)-6-Methoxy-a-methyl-2-naphthalene)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

25 2-(α,α,α -Trifluoro-3-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(α,α,α -Trifluoro-2-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-((S)-(+)-4-Isobutyl- α -methylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

5 2-(3,4,5-Trimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

10 2-(2-Amino 4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N,N-Dimethylsulfonamido-2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide; 2-

15 2-(2-Amino,x,x,x-Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-N,N-Dimethylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

20 2-(N-Methylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

25 2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Hydroxyphenyl)-N-methyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide; and

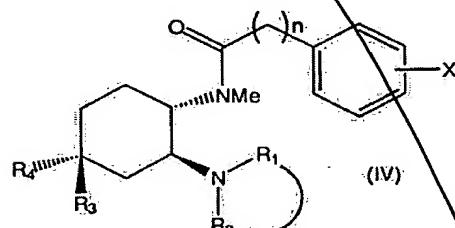
N-Methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidine-1-yl)ethyl]-3,4,5-trimethoxyphenylacetamide.

5 16. A method for the prevention or treatment of pruritus in a patient comprising
administering to said patient an effective amount of a composition according to claim 13.

17. A method for the prevention or treatment of pruritus in a patient comprising
administering to said patient an effective amount of a composition according to claim 14.

18. A method for the prevention or treatment of pruritus in a patient comprising
10 administering to said patient an effective amount of a composition according to claim 15

19. A pharmaceutical composition for the prevention or treatment of pruritus comprising
a compound of the formula IV or a pharmaceutically acceptable salt thereof



wherein

15 n = 1-3;

R₁ and R₂ are independently = CH₃; -(CH₂)_m, where m =

4-8, -CH₂CH(OH)(CH₂)₂-; -CH₂CH(F)(CH₂)₂-;

-(CH₂)₂O(CH₂)₂-; or -(CH₂)₂CH=CHCH₂-;

R₃ and R₄ are independently H; OCH₃ alkyl; or c-O(CH₂)₂

20 X₉ = 1-4 substituents selected from the groups consisting of

-halogen; -CF₃; -OCH₃; -SO₂NH(CH₂)_qCO₂H; CONH(CH₂)_qCO₂H;

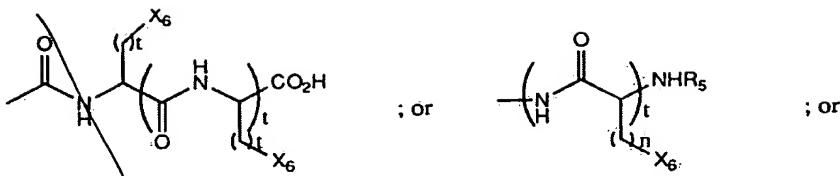
-NH₂; -NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂; NH(CH₂)_qCO₂H; -SO₂CH₃

-OP(O)(OBn)₂; -OP(O)(OH)₂; -CO₂H; O(CH₂)_qCO₂H; -O(CH₂)_qSO₃H; ;

-O(CH₂)_qOPO₃H₂; wherein

25 q = 1-20;

or X₉ is



wherein

t = 1-20;

R₅= -H or -Ac

$X_5 = -CO_2H; -NHSO_2CH_3; -NHP(O)(OBn)_2;$

-NHP(O)(OH)₂; -OP(O)(OBn)₂; or
-OP(O)(OH)₂

in a pharmaceutically acceptable vehicle.

20. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

10 (--)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-methanesulfonamido)aminophenylacetamide; (--)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)sulfonamidophenylacetamide; and (--)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)carboxamidophenylacetamide.

15 21. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

(±)-trans-2-Nitro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

Hydrochloride;

(\pm)-*trans*-2-Amino-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

20 Hydrochloride;

(\pm)-*trans*-2-Nitro-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-trans-2-Amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

25 (\pm)-*trans*-2-Methanesulfonamido-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

N-[2-(\pm)-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride;

(\pm)-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

5 (\pm)-*trans*-2-Nitro-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-2-Bismethanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

10 (\pm)-*trans*-2-Methanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

N-[2-(\pm)-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride;

15 (\pm)-*trans*-3-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-5-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-2-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

20 (\pm)-*trans*-2-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-4-Nitro-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

25 (\pm)-*trans*-4-Amino-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(\pm)-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]2,2-diphenylacetamide Hydrochloride;

and

(\pm)-*trans*-4-Methylsulfonyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide Hydrochloride.

22. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 19.

23. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 20.

24. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 21.

*Add
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